REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

The claims are amended to recite specific embodiments. In particular, claim 1 is amended to recite methods of treatment for mastalgia using "a composition comprising 4-hydroxy tamoxifen as the sole therapeutically active ingredient." Conforming amendments are made to other claims. These amendments are fully supported by the application as filed, which plainly conveys to the skilled artisan Applicant's possession of a method for treatment of mastalgia using a composition comprising 4-hydroxy tamoxifen as the sole therapeutically active ingredient. *See, e.g.,* paragraphs [0008] and [0028] – [0030].

These amendments are made without prejudice or disclaimer, and Applicant reserves the right to pursue any canceled subject matter in one or more continuing applications with the same rights of priority as the instant application.

Upon entry of these amendments, claims 1-4 and 6-14 will remain pending. These claims are presented for reconsideration.

The Patent Office Interview

Applicant thanks Examiner Ramachandran and Padmanabhan for the courtesies extended during the Patent Office Interview on October 6, 2009. Applicant's statement of the substance of the interview is provided here, in accordance with MPEP § 713.04. As noted on the Interview Summary, the Examiners suggested that Applicant consider amending the claims to recite that 4-OHT is the sole therapeutically active ingredient in the composition used to treat mastalgia. Although Applicant does not agree that the previously pending claims are not patentable, in order to advance prosecution the foregoing amendments reflect the Examiners' suggestion. During the Interview, Applicant also discussed the background of the invention (*e.g.*, benign breast disease) and the teachings of the cited references, and explained that the claimed methods are patentable thereover. These points are outlined again below.

The Obviousness Rejections

The claims are rejected for alleged obviousness over (i) U.S. 4,919,937 (the Mauvais-Jarvis patent); (ii) Mauvais-Jarvis, *Current Therapy in Endocrinology Metabolism* (1988); (iii) Mauvais-Jarvis, *Senologies et Pathologie* (1986); (iv) Pujol (1995) and (v) Fentiman (1988). Additionally, Malet (1988) and U.S. 5,613,958 (Kochinke) are cited against claims 4 and 9, respectively. Applicant respectfully traverses the obviousness rejections for the reasons discussed in the Patent Office Interview and set forth below.

Applicant notes that page 17 of the Office Action confirms that the Fentiman reference is cited only for teaching that mastalgia can be cyclical, and that "the rejection is not based on substituting 4-OH[T] for tamoxifen." Indeed, Applicant's previous response and the Hilt Declaration submitted therewith demonstrate that the use of oral tamoxifen to treat mastalgia in no way suggests the present invention, even under an "obvious to try" standard, because of the unpredictability surrounding tamoxifen and its many different metabolites, and the lack of a predictable correlation between the anti-estrogen activity of a tamoxifen metabolite and its clinical efficacy. *See, e.g.*, Hilt Declaration, ¶¶ 11-13 and 19-24.

Applicant also notes that the two Mauvais-Jarvis papers (Mauvais-Jarvis (1988) and Mauvais-Jarvis (1986)) are largely, although not entirely, identical.

Benign Breast Disease & Mastalgia

As discussed during the Patent Office Interview, "benign breast disease" is an umbrella term that encompasses a number of different benign (non-cancerous) breast conditions. While mastalgia (breast pain) generally is considered to be ***a*** benign breast disease, "benign breast disease" encompasses other conditions, including nonproliferative lesions, increased nodularity, fibroadenomas, cysts and fibrocystic disease. *See, e.g.*, Mauvais-Jarvis (1988), Introduction and Table 2. Not all patients suffering from benign breast disease experience mastalgia. To the contrary, Plu-Bureau et al., *Cancer Epidemiol. Biomarkers Prev.* 15: 1229-31 (2006) (submitted herewith) studied a population of benign

breast disease patients where only 77 out of 247 subjects suffered from mastalgia. *See, e.g.,* Plu-Bureau, Table 1. Thus, a person skilled in the art would not understand the term "benign breast disease" to necessarily mean mastalgia. At best, mastalgia is a particular species of the genus of benign breast disease conditions.

The Mauvais-Jarvis References Do Not Suggest The Claimed Methods

The Mauvais-Jarvis patent is the primary reference cited in the obviousness rejections, and is particularly cited for its teaching that 4-OHT can be used to treat benign breast disease. The only relevant passage in the Mauvais-Jarvis patent is at column 4, lines 37-39, which states:

> The drug described finds application in the treatment of conditions of the breast, especially benign and even cancerous conditions of the breast.

This is a general teaching that does not specifically implicate mastalgia. Indeed, neither mastalgia nor breast pain are mentioned anywhere in the Mauvais-Jarvis patent. Thus, the Mauvais-Jarvis patent provides no suggestion that 4-OHT might be useful against the particular benign breast condition at issue here. Indeed, as noted in the Hilt Declaration submitted previously, the Mauvais-Jarvis patent does not include any experimental data showing that 4-OHT is effective against any benign breast condition. *See, e.g.*, Hilt Declaration ¶30 (discussing breast density in particular).

The Mauvais-Jarvis papers further underscore the separate treatment of different benign breast conditions. Both Mauvais-Jarvis papers provide a review of proposed therapies for treating different benign breast disease conditions, including (i) mastalgia, (ii) breast abnormalities (e.g., nodes, fibroadenomas, cysts and fibrocystic disease) and (iii) breast cell multiplication. Mauvais-Jarvis (1986), page 128; Mauvais-Jarvis (1988), page 280, col. 2. The papers note that a dopamine agonist that was "proposed for the treatment of benign breast disease, particularly in the case of mastodynia [mastalgia]" has not been shown to be effective. The papers discuss several candidates that are "anti-estrogens," including tamoxifen and 4-OHT, but do not teach that any are effective against any benign breast disease condition, let alone mastalgia in particular. On the other hand, the papers do report

that percutaneous progesterone has been shown to achieve "complete disappearance of breast pain," and improvement in other benign breast conditions (such as nodularity) when administered in conjunction with an oral progestin. Mauvais-Jarvis (1986), page 130; Mauvais-Jarvis (1988), page 282, col. 2 – page 283, col. 1 and Table 2.

Thus, the skilled artisan reviewing the Mauvais-Jarvis papers would understand them to be teaching that ***percutaneous progesterone*** could be used to treat mastalgia, and would not understand them to suggest the use of 4-OHT in that context. Indeed, the 4-OHT sections of these papers refer generally to the use of "4-OHT alone or ***in combination with a progestin***," and note that "[t]his possible therapeutic approach is under investigation." Mauvais-Jarvis (1986), page 130; Mauvais-Jarvis (1988), page 281, col. 2 (emphasis added). The Mauvais-Jarvis patent also emphasizes the use of 4-OHT in a composition that also comprises progesterone, with the only exemplary formulation including ***both*** 4-OHT ***and progesterone***.

Mauvais-Jarvis (1988) also demonstrates that a therapeutic agent useful against one benign breast disease condition may not necessarily be useful against other benign breast disease conditions. For example, while percutaneous progesterone was reported to be effective against mastalgia when used alone (75% response rate), it showed only minimal efficacy against nodularity (10% response rate) and no efficacy (0%) against fibroadenomas, cysts, or fibrocystic disease. Mauvais-Jarvis (1988), page 283, Table 2.

Taken as a whole, these references establish that the skilled artisan would not have understood the general statement in the Mauvais-Jarvis patent as a teaching or suggestion that 4-OHT could or should be used to treat mastalgia in particular. Moreover, given the patent's emphasis on 4-OHT/progesterone combinations, it certainly would not suggest a method as claimed, which uses a composition comprising 4-OHT as the sole therapeutically active ingredient to treat mastalgia. Indeed, the Mauvais-Jarvis patent teaches in column 4 that while a 4-OHT/progesterone combination "is capable of blocking in vitro the activity of estrogens . . . and at the same time improving the progesterone activity," those results "are ***not achieved with the separate administration of each of the constituents***" (emphasis added). Thus, the cited references do not suggest the presently claimed invention.

Pujol Does Not Suggest The Claimed Dosages

The Office Action asserts in several different places that Pujol teaches the percutaneous application to the breast of dosages of 4-OHT recited in the claims (at least 1.5 mg/day). This is simply not correct. In Pujol's studies, ***the maximum dose applied to breast areas was 1 mg/day (total)***. Higher doses (including 2 mg/day total) were applied to "a large cutaneous area excluding the breasts." Pujol. Page 494, col. 1-2. As discussed during the Patent Office Interview, the Pujol study is described in the instant application, which plainly teaches that only 0.5 mg/day (0.25 mg/breast) or 1.0 mg /day (0.5 mg/breast) were applied to breast areas in that study. *See, e.g.,* paragraph [0041] and Table 3 of the instant application. As taught in the application and discussed in Applicant's previous response, Applicant determined that such doses are ineffective against mastalgia. *See, e.g.* Example 4, paragraphs [0063] – [0065] and Tables 8 and 9.

The Office Action also appears to assume that Pujol found that its dosages of 4-OHT were effective against breast cancer. Again, this is simply not correct. As explained previously and stated plainly in Pujol, Pujol reported that "at the doses described in this report, 4-OH-TAM is not an alternative method of chemoprevention." Pujol, page 497, col. 2. Likewise, in the Abstract, Pujol states that "at the doses described in this study, percutaneous 4-OH-TAM cannot be proposed as an alternative tamoxifen treatment." Thus, Pujol provides no reason to expect that percutaneous 4-OHT would be useful against its target condition (breast cancer), let alone the completely different condition recited in the instant claims (mastalgia).

The Office Action asserts that "[d]osage is clearly a result effective parameter that can be routinely optimized . . . . Hence it would have been obvious . . . to have used 1.5 mg/day or 2.0 mg/day of 4-OHT in expectation of obtaining therapeutic benefits in a method of treating a breast condition such as mastalgia." This assertion is illogical and not supported by any evidence of record. How could a teaching that certain doses of 4-OHT were ***not effective*** against one condition make it obvious to use a higher dose to treat a ***different condition***? Moreover, this assertion overlooks the fact that Pujol did study higher doses of 4-OHT (although not administered to breast areas) and found none to be effective.

As explained in Applicant's previous response, the recited dosages have clinical significance, as illustrated by the data reported in the specification, in Example 4 at pages 20-22. The reported data show that the percutaneous application of 4-OHT to breasts at doses of 0.5 mg/day or 1.0 mg/day is ***not effective against mastalgia***. On the other hand, when a dose of at least 1.5 mg/day is applied to breasts, as recited in the claims, the results are effective, whether assessed by mean pain intensity or duration of pain.

In summary, there is no teaching or suggestion in the cited references that would have led the skilled artisan to administer percutaneously to the breasts of a patient having mastalgia a composition comprising 4-hydroxy tamoxifen as the sole therapeutically active ingredient, at a dose of at least 1.5 mg/day 4-hydroxy tamoxifen, in order to treat mastalgia, as recited in the instant claims.

The further secondary references—Fenitman, Malet and Kochinke—do not remedy the inability of the Mauvais-Jarvis references and Pujol to suggest the methods recited in independent claim 1. For example, Fentiman is cited for teaching that mastalgia can be cyclical, Malet is cited for teaching that the "trans" isomer of 4-OHT has stronger antiproliferative effects than the "cis" isomer, and Kochinke is cited for teaching a composition comprising isopropyl myristate, ethanol and hydroxypropylcellulose. These references do not have any direct bearing on the non-obviousness of a method for the treatment of mastalgia using 4-OHT.

For at least the foregoing reasons, Applicant respectfully urges reconsideration and withdrawal of the obviousness rejections.

The Obviousness-Type Double Patenting Rejections

The claims are rejected under the doctrine of obviousness-type double patenting over claims 1-9 of U.S. 7,507,769, in view of Mauvais-Jarvis (1988). Without acquiescing on the merits, Applicant submits herewith a Terminal Disclaimer in order to obviate this rejection.

Claim 1 is provisionally rejected under the doctrine of obviousness-type double patenting over claim 18 of co-pending U.S. Application 11/249,122. Applicant notes that

U.S. Application 11/249,122 was filed after the instant application. Therefore, when this provisional obviousness-type double patenting rejection is the only issue remaining in the instant application, it should be withdrawn in this application and entered or maintained (if appropriate) in U.S. Application 11/249,122. *See* MPEP § 804 ("If a 'provisional' nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.").

Conclusion

Applicant believes that the present application is now in condition for allowance, and an early notice to that effect is earnestly solicited.

Should there be any questions regarding this submission, or should any issue remain, the Examiner is invited to contact the undersigned by telephone in order to advance prosecution.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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